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LETTER TO THE EDITOR

Small fiber neuropathy underlying dysautonomia in COVID-19 and in post-SARS-CoV-2 vaccination and long-COVID syndromes

We eagerly read the excellent editorial by Gemignani and the corresponding original article by Abrams et al. about the suspected involvement of small fibers (small fiber neuropathy [SFN]) in acute severe, acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and in long-coronavirus disease (COVID) syndrome.[1,2] It was speculated that at least some of the clinical manifestations of long-COVID syndrome could be attributed to involvement of small nerve fibers by the viral infection. The authors believe that studies are needed that investigate the role of autonomic dysfunction in long-COVID syndrome and the prevalence of SFN by means of the 13-item SFN symptom inventory questionnaire. The papers are appealing but raise some concerns that require discussion.

I do not agree with the notion that long-COVID syndrome is the same as post-COVID syndrome.[1] Acute COVID-19 usually lasts one to 4 wk. Subacute COVID-19 lasts 5 to 12 wk. When clinical manifestations of COVID-19 persist beyond 12 wk, the condition is termed post-COVID syndrome. Both subacute COVID-19 and post-COVID syndrome are included under the overarching term long-COVID-syndrome. Differentiating long-COVID syndrome from post-COVID-syndrome is crucial for their management and for assessing long-term outcomes.

An issue not addressed in the paper is Guillain-Barre syndrome (GBS) due to an infection with SARS-CoV-2.[3] There is ample evidence that the immune response to the virus can trigger autoimmune reactions, including those that are involved in the development of GBS. There is evidence accumulating that mRNA- and vector-based anti-SARS-CoV-2 vaccines can trigger the development of GBS.[4] GBS can affect not only motor and sensory fibers, but also peripheral autonomic fibers, particularly in the GBS subtype of acute motor and sensory axonal neuropathy (AMSAN). There is a subtype of GBS that may exclusively affect autonomic fibers and present with pure dysautonomia.[5] Because GBS may be mild, it can go unrecognized; because patients often have a long recovery time, autonomic manifestations in long COVID syndrome could be explained by incomplete recovery from autonomic involvement in abortive GBS.

Not addressed in the articles is the involvement of the central autonomic nervous system (ANS). There are several reports demonstrating that a SARS-CoV-2 infection can be complicated by hypophysitis.[6] Furthermore, patients with a pre-existing pituitary micro- or macro-adenoma have an increased risk of pituitary apoplexy during SARS-CoV-2 infection.[7] Accordingly, the hypophysial-pituitary-adrenergic axis can be impaired,[8] thus leading to autonomic dysfunction.

Autonomic dysfunction may not always be recognized by those involved in the management of COVID-19 patients. Thus, patients with SARS-CoV-2 infection are often not investigated sufficiently for their symptoms of autonomic dysfunction, such as insomnia, fatigue, cognitive impairment, hypersensitivity to light, blurred vision, dry eyes or mouth, drooling, palpitations, syncope, orthostatic dizziness, hot flashes, dysphagia, bowel or bladder dysfunction, sexual dysfunction, changes in skin, hair, and nails, or abnormalities of sweating. Studies that may be performed to assess ANS involvement are a contrast-enhanced magnetic resonance imaging (MRI) of the pituitary gland, determination of releasing factors, pituitary stimulating hormones, and hormones of peripheral endocrine organs, and diagnostic testing for involvement of the peripheral ANS. Several of the latter tests are not widely available and their sensitivity and specificity may be low if portions of the peripheral ANS are tested that are not affected.

Not addressed was the role of anti-COVID-19 drugs in the development of SFN. There is increasing evidence that some of the compounds administered to infected patients are neurotoxic and can be responsible for polyneuropathy. Some of these compounds, such as lopinavir, ritonavir, daptomycin, and linezolid, may also damage autonomic fibers.

I agree that there is a need to investigate the involvement of the central and peripheral ANS in some patients with acute SARS-CoV-2 infections or long-COVID syndrome. Such patients should be investigated not only by use of questionnaires and the Quantitative Sudomotor Axon Reflex Test (QSART) but particularly by quantitative sensory testing (QST), microneurography of C-fibers of the superficial peroneal nerve, sensory stimulation tests, the deep breathing test, the Valsalva

List of abbreviations: AMSAN, Acute motor and sensory axonal neuropathy; ANS, autonomic nervous system; CCM, corneal confocal microscopy; CHEP, contact heat-evoked potentials; COVID, coronavirus disease; GBS, Guillain-Barre syndrome; LASCA, laser speckle contact analysis; MRI, magnetic resonance imaging; PGP, protein gene product; PREP, pain-related evoked potentials; QSART, Quantitative Sudomotor Axon Reflex Test; QST, quantitative sensory testing; SARS-CoV-2, severe, acute respiratory syndrome coronavirus 2; SFN, small fiber neuropathy.

maneuver, tilt testing, cerebral blood flow velocity measurements, pain-related evoked potentials (PREP), laser speckle contact analysis (LASCA), laser Doppler flowmetry, laser Doppler imaging, contact heat-evoked potentials (CHEP), corneal confocal microscopy (CCM), and proximal or distal skin biopsy stained with protein gene product (PGP) 9.5. Furthermore, hormone levels should be determined and autopsy of COVID-19 patients should include histological investigations of central and peripheral autonomic pathways.

KEYWORDS

adverse reactions, COVID-19, SARS-CoV-2, side effects, vaccination

CONFLICTS OF INTEREST

None.

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AUTHOR CONTRIBUTION

JF: design, literature search, discussion, first draft, critical comments, final approval.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

All data are available form the correspndong author

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